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Published
*With international search report.*

(54) Title: DEPRENYL FOR SYSTEMIC TRANSDERMAL ADMINISTRATION

(57) Abstract

SELEGILINE

N-methyl-N-(1-phenyl-2-propyl)-2-propinylamine in racemic or optically active form and the pharmaccutically acceptable acid addition salts thereof are useful for systemic transdermal administration.

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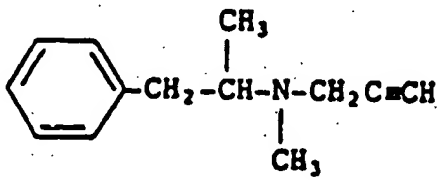
# Deprenyl for systemic transdermal administration.

The present invention provides the systemic transdermal application of deprenyl.

Deprenyl[N-methyl-N-(1-phenyl-2-propyl)-2-propinylamine] of formula I



I

has been disclosed in the literature as a monoamine oxidase inhibitor. The preparation of the racemic mixture is described e.g. in Fr. pat. M 2635, whereas Dutch Patent Application 6,605,956, for instance, discloses the (-)-form of the compound (also known as L-Deprenil, L-Deprenaline or Selegiline). The antidepressive and antiparkinson activity of the racemate and the (-)-form have been reported in various publications.

It has now surprisingly been found that the compound of formula I in racemic or optically active form as well as the pharmaceutically acceptable acid addition salts thereof, hereinafter referred to as compounds for administration according to the invention, exhibit unexpectedly good skin penetration when administered percutaneously.

The penetration through the skin of the compounds for administration according to the invention may be observed in standard in vitro or in vivo tests.

One in vitro test is the well known diffusion test which may be effected according to the principles set out in GB 2098865 A and by T.J. Franz in J. Invest. Dermatol. (1975) 64, 194 - 195. The composition containing the active agent in unlabelled or radioactively labelled form is applied to one side of isolated pieces of intact human skin or hairless rat skin about 2 $cm^2$ in area. The other side of the skin is in contact with physiological saline. The amount of active agent in the saline is measured in conventional manner, e.g. by HPLC or spectrophotometric techniques, or by determining the radioactivity.

In this test using rat skin the following penetration rates, for example, have been found:

| | | | |
|---|---|---|---|
| Composition 1: | Compound of formula I | | |
| (solution) | in (-)-form as hydrochloride | 35 | mg |
| | Ethanol | 970 | mg |
| | Polyol-polyether-fatty acid ester, e.g. Cetiol HE* | 30 | mg |

| | | | |
|---|---|---|---|
| Comp sition 2: | Compound of formula I | | |
| (p lymer film) | in (-)-form as hydrochloride | 10 | % |
| | Hydroxypropylcellulose, | | |
| | e.g. Klucel LF* | 90 | % |
| Composition 3: | Compound of formula I | | |
| (solution) | in (-)-form as hydrochloride | 7.3 | mg |
| | Ethanol | 0.2 | ml |
| | Isopropylmyristate | ad 1.0 | ml |

* : Registered Trade Mark

| | Penetration rates (24 h) | | | | | |
|---|---|---|---|---|---|---|
| | Receptor medium | | Skin | | Total | |
| | % | mg/cm² | % | mg/cm² | % | mg/cm² |
| Composition 1 | 5.2 | 0.267** | 1.3 | 0.067 | 6.5 | 0.334 |
| Composition 2 | 4.3 | 0.022 | 0 | 0 | 4.3 | 0.022 |
| Composition 3 | 36.1 | 0.434 | 8.2 | 0.098 | 44.3 | 0.532 |

**: Corresponds to $6.0 \times 10^{-4}$ mole/cm²/hour

Moreover it has been found that transdermal administration of the compounds for administration according to the invention induces a long-lasting and constant inhibition of monoamine oxidase activity as indicated in standard tests, with a slov onset of action, which is particularly advantageous with respect to the tolerability of these compounds.

Thus the present invention provides a pharmaceutical composition for systemic transdermal administration incorporating as active

ag nt the compound f f rmula I in racemic or optically active form or a pharmaceutically acceptable acid addition salt thereof.

Preferably such a pharmaceutical composition has a penetration rate of at least $10^{-9}$ mole/cm²/hour, more preferably of at least $10^{-8}$ mole/cm²/hour. Suitably the penetration rate after 24 hours is at least 3 %, preferably at least 10 %.

The compound of formula I is preferably present in (-)-form and as hydrochloride.

In a further aspect the present invention provides the use of the compound of formula I in racemic or optically active form or a pharmaceutically acceptable acid addition thereof, as active agent in the manufacture of a pharmaceutical composition suitable for systemic transdermal administration.

In yet a further aspect the present invention provides a method of systemically administering the compound of formula I in racemic or optically active form or a pharmaceutically acceptable acid addition salt thereof, which comprises applying a pharmaceutical composition according to the invention onto the skin.

The active agent may be administered in any conventional liquid or solid transdermal pharmaceutical composition, e.g. as described in Remington's Pharmaceutical Sciences 16th Edition Mack; Sucker, Fuchs and Spieser, Pharmazeutische Technologie 1st Edition, Springer and in GB 2098865 A or DOS 3212053 the contents of which are incorporated herein by reference.

Conveniently the composition is in the form f a viscous liquid, ointment or solid reservoir r matrix. For example the active agent is dispersed thr ughout a solid reservoir or matrix made of

a gel or a solid polymer, e.g. a hydrophilic polymer as described in European Patent Application No. 155,229.

The active agent may be incorporated in a plaster.

The compositions for transdermal administration may contain from about 1 to about 50 % by weight of active agent.

The pharmaceutical compositions for transdermal administration may be used for the same indications as for oral or intravenous administration. The amount of pharmaceutically active agent to be administered will individually depend on the drug release characteristics of the pharmaceutical compositions, the drug penetration rate observed in in vitro and in vivo tests, the potency of active agent, the size of the skin contact area, the part of the body to which the unit is stuck, and the duration of action required. The amount of active agent and area of the pharmaceutical composition etc. may be determined by routine bioavailability tests comparing the blood levels of active agents after administration of the active agent in a pharmaceutical composition according to the invention to intact skin and blood levels of active agent observed after oral or intravenous administration of a therapeutically effective dose of the pharmacologically active agent.

Given the daily dose of a drug for oral administration, the choice of a suitable quantity of drug to be incorporated in a transdermal composition according to the invention will depend upon the pharmacokinetic properties of the active agent, taking into account that there is no first pass effect; the amount of drug which can be absorbed through the skin from the matrix in question for a given area of application and in a given time; and the time for which the composition is to be applied. Thus, a drug with a high first pass effect may require a relatively low

quantity in the transdermal comp sition when compared with the oral daily dose, since the first pass effect will be avoided. On the other hand, generally a maximum of only approximately 50 % of the drug in the matrix is released through the skin in a 3 day period.

The pharmaceutical compositions of the invention in general have for example an effective contact area of drug reservoir on the skin of from about 1 to about 50 square centimetres, preferably about 2 to 20 square centimetres, and are intended to be applied for from 1 - 7 days, preferably 1 - 3 days.

Unit dosage forms preferably contain from about 1 mg to about 50 mg of the compound for administration according to the invention.

The compounds for administration according to the invention may for example be administered at a dose of 10 mg in a patch of ca. 10 $cm^2$, once every three days.

The compositions according to the invention may contain further active substances, e.g. further agents which exhibit activity in the treatment of Parkinson's disease, such as levodopa or bromocriptine, or agents with antidepressive activity such as l-phenylalanine. They may thus be used for the treatment of various conditions including Parkinson's disease and depression.

The compositions according to the invention are preferably used for the treatment of Parkinson's disease. The present invention thus more particularly provides a method of treating a subject suffering from Parkinson's disease, wherein a pharmaceutical composition of the invention is applied onto the skin.

The folloving example illustrates the invention.

**EXAMPLE: Preparation of a transdermal composition containing a hydrophilic polymer**

**Composition**

| | |
|---|---|
| Compound of formula I in (-)-form as hydrochloride | 20 % |
| Hydrophilic polymer, e.g. Eudragit E 100* | 30 % |
| Non swellable acrylate polymer, e.g. Durotack 280 - 2416** | 44 % |
| Plasticizer, e.g. Brij 97*** | 6 % |

* : Registered Trade Mark, available from Röhm, Darmstadt, W. Germany

** : Registered Trade Mark, available from Delft National Chemie Zutphen, Netherlands

***: Registered Trade Mark, available from Atlas Chemie, W. Germany

The components are added to acetone or ethanol or another appropriate volatile organic solvent and mixed to give a viscous mass. The mass is spread on top of an aluminised polyester foil (thickness 23 microns) using a conventional apparatus, to produce a film of thickness 0.2 mm when wet. The film is alloved to dry at room temperature over 4 to 6 hours. The aluminium foil is then cut up into patches about 10 sq cm in area.

WHAT WE CLAIM IS:

1. A pharmaceutical composition for systemic transdermal administration, incorporating as active agent N-methyl-N-(1-phenyl-2-propyl)-2-propinylamine in racemic or optically active form or a pharmaceutically acceptable acid addition salt thereof.

2. A pharmaceutical composition according to claim 1, wherein the active agent is the hydrochloride of the (-)-form.

3. A pharmaceutical composition for systemic transdermal administration, substantially as hereinbefore described with reference to the Example.

4. The use of N-methyl-N-(1-phenyl-2-propyl)-2-propinylamine in racemic or optically active form or a pharmaceutically acceptable acid addition salt thereof, as active agent in the manufacture of a pharmaceutical composition suitable f r systemic transdermal administration.

5. The use of the (-)-N-methyl-N-(1-phenyl-2-propyl)-2-propinylamine-hydrochloride, as active agent in the manufacture of a pharmaceutical composition according to claim 2.

6. The use of N-methyl-N-(1-phenyl-2-propyl)-2-propinylamine in racemic or optically active form or a pharmaceutically acceptable acid addition salt thereof, as active agent in the manufacture of a pharmaceutical composition suitable for systemic transdermal administration in the treatment of Parkinson's disease.

7. The use f the (-)-N-methyl-N-(1-phenyl-2-propyl)-2-propinylamine-hydrochloride, as active agent in the manufacture of a pharmaceutical composition according to claim 2, for the treatment of Parkinson's disease.

8. A method of systemically administering N-methyl-N-(1-phenyl-2-propyl)-2-propinylamine in racemic or optically active form or a pharmaceutically acceptable acid addition salt thereof, which comprises applying a pharmaceutical composition according to claim 1 onto the skin.

9. A method of systemically administering the (-)-N-methyl-N-(1-phenyl-2-propyl)-2-propinylamine-hydrochloride, which comprises applying a pharmaceutical composition according to claim 2 onto the skin.

10. A method of treating a subject suffering from Parkinson's disease wherein a pharmaceutical composition according to claim 1 is applied onto the skin.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 89/00291

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 31/135; A 61 L 15/03

## II. FIELDS SEARCHED

Minimum Documentation Searched [7]

| Classification System | Classification Symbols |
|---|---|
| IPC[4] | A 61 K; A 61 L |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

## III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

| Category [10] | Citation of Document, [11] with indication, where appropriate, of the relevant passages [12] | Relevant to Claim No. [13] |
|---|---|---|
| Y | Martindale, The Extra Pharmacopoeia, 28th edition, 1982, edited by James E.F. Reynolds et al., publ. by The Pharmaceutical Press, (London, GB), pages 1752-1753 see pages 1752-1753, "Selegiline hydrochloride" -- | 1-7 |
| Y | US, A, 4568343 (H. LEEPER) 4 February 1986 see column 2, line 67 -- | 1-7 |
| Y | GB, A, 2163347 (STATE OF ISRAEL INSTITUTE FOR BIOLOGICAL RESEARCH) 26 February 1986 see page 1, lines 5-20, table 1; page 2, lines 35-42; claim 12 -- | 1-7 |
| Y | EP, A, 0139127 (F. HOFFMANN-LA ROCHE & CO.) 2 May 1985 see page 5, lines 35-36 -- ./. | 1-7 |

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 10th May 1989 | 12 JUN 1989 |
| **International Searching Authority** | **Signature of Authorized Officer** |
| EUROPEAN PATENT OFFICE | P.C.G. VAN DER PUTTEN |

International Application No. PCT/EP 89/00291

FURTHER INFORMATI N CONTINUED FR M THE SECOND SHEET

| | | |
|---|---|---|
| Y | Psychopharmacol. Bull., volume 21, no. 3, 1985, C.R. Gardner: "Targeting the central nervous system: new drug delivery technologies for psychotropic agents", pages 657-662 see the whole article -- | 1-7 |
| Y | Movement Disorders, volume 2, no. 3, 1987, Movement Disorder Society, W. Koller et al.: "PHNO, a novel dopamine agonist, in animal models of Parkinsonism", pages 193-199 see page 196 --------- | 1-7 |

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 8-10, because they relate to subject matter not required to be searched by this Authority, namely:

See PCT-rule 39.1 (iv): methods for treatment of the human or animal body by surgery or therapy as well as diagnostic methods

2. [ ] Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 8900291 SA 27512

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 08/06/89
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| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| US-A- 4568343 | 04-02-86 | None | |
| GB-A- 2163347 | 26-02-86 | CH-B- 667393 | 14-10-88 |
| | | DE-A- 3528979 | 27-02-86 |
| | | FR-A,B 2569112 | 21-02-86 |
| | | JP-A- 61186317 | 20-08-86 |
| | | SE-A- 8503664 | 15-02-86 |
| | | US-A- 4788063 | 29-11-88 |
| EP-A- 0139127 | 02-05-85 | JP-A- 60058913 | 05-04-85 |